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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732,669	12/08/2000	Todd A. Blumenkopf	PC10609ABTC	2857

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EXAMINER	
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ART UNIT	PAPER NUMBER
1624	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/732,669	BLUMENKOPF ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22 and 25-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22 and 25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' response, which included cancellation of claims 21, 23-24, amendment to claims 1, 19, 20, 22, 26 and addition of new claims 27-31 filed 10/28/2002, is made of record.

Claims 1-20, 22, 25-31 are now pending.

Specification

The amendment filed on 10/25/2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicants have modified several lines in page 2 and 3, which alters the definition of heterocycloalkyl and heteroaryl. The scope of these groups are now broader than what was originally presented. Applicant is required to cancel the new matter in the reply to this Office Action.

The following rejections made in the previous office action remain.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20, 22 and 25-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Recitation of the term " alkyl" in claim 1 is indefinite as specification on page 5 offers two distinct definitions for the same term. The term " alkyl" is defined on page 5, line 12-14 differs from that is recited in lines 22-27 which not only include cyclic alkyl with examples as several cycloalkyls but also halogen substituents. It is not clear what is difference between "alkyl" and "cycloalkyl" recited in the claims.

   This rejection is same as made in the previous office action. Applicants' argument to overcome this rejection is not persuasive. There are two distinct definitions. Cycloalkyl is an alkyl in one hand and in the other hand it is a cyclic alkyl. This creates ambiguity. Hence the rejection is maintained.

2. Recitation of "cancer leukemia" in claims 27 and 29 renders these claims indefinite as these claims recite the broad recitation "cancer", and the claim also recites "leukemia" which is the narrower statement of the range/limitation in the sense "such as" or " for example". Note the phrase "such as" or "for example" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

3. In claim 22, the term " transplation" appears to be misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22,25-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating psoriasis, does not reasonably provide enablement for treating or preventing all diseases embraced in the instant invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is same as made in the previous office action except that the newly added claims 27-30 are also included and cancelled claims 21, 23-24 are excluded herein. To repeat:

Method claims 25-26, 29-30 and pharmaceutical composition claims 22, 27 with intended uses are not adequately enabled for the range of diseases recited therein. From the reading of specification, it appears that the applicants are asserting that the embraced compounds because of their mode action, which involves inhibition of Janus family of tyrosine kinase(s), would be useful for all sorts of diseases including autoimmune diseases, cancer, Alzheimer's disease, various arthritis, multiple sclerosis etc. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended mammal. Moreover many if not most of diseases such as rheumatoid arthritis, sepsis, chronic hepatitis, multiple sclerosis, Alzheimer's disease etc. are very difficult to treat and hardly possible to prevent as claimed herein. For multiple sclerosis alone there is no known drug, which can successfully reverse the course of the disease, despite the fact that there are many drugs, which can be used for "inflammatory condition". Note substantiation of utility and its scope is required when

utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

The instant claims are drawn to 'a method for treating or preventing a disorder or condition selected from organ transplant rejection, lupus multiple sclerosis rheumatoid arthritis etc. The scope of the claims includes not only treatment but also "prevention of a disease" which is not adequately enabled solely based on the activity of the compounds as tyrosine kinase or Janus kinase 3 inhibitors provided in the specification at pages 25-26. "To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Traxler (provided).

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating or preventing all diseases due to tyrosine kinase inhibitory activity.

2) The state of the prior art: Although there are several tyrosine kinase inhibitors known, they have not prevented or able to treat all diseases embraced in the instant claims. 3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the 'preventive' effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There is no supporting evidence that all diseases embraced are treatable and even preventable in view of their tyrosine kinase activity.

6) The breadth of the claims: The instant claims embrace not only treatment but also the prevention of diseases.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards 'preventing' the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Applicants' argument to overcome this rejection is not persuasive.

1. As for applicants argument that " considerable amount of experimentation is permissible" is not valid, as applicants have not provided any evidence that by mere routine experimentation one can treat or prevent all diseases. Prior art search does not support applicants' contention. Furthermore as noted in the previous office action some of these disease are even difficult to treat. Thus one trained in the art were to do any undue experimentation to arrive at a enablement for treating and preventing these diseases, it cannot be applicants' invention as the findings cannot be deemed as applicants' findings since there is no enabling

disclosure for treating and or preventing all diseases embraced in the instant claims. The fact that single class of compounds can treat and or prevent all diseases embraced in these claims is really remarkable for which applicants have not provided any supporting evidence.

2. As stated in the previous office action, "To prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Websters II Dictionary). Applicants' have not provided any evidence that this is the case with instant invention.

Hence this rejection is proper and is maintained.

Claims 1-20, 22 and 25-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' amendment to claims to change the definition of heterocycloalkyl and heteroaryl has resulted in broader scope than what was originally claimed. See changes to these groups and compare it with the originally presented definition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 22, 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cockerill et al. WO 98 02438 for reasons of record.

Applicants' argument to overcome this rejection is not persuasive.

1. First of all, applicants' argument that examiner had not made a prime facie case is incorrect. The rejection is based on proper factual analysis. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

    1. Determining the scope and contents of the prior art.
    2. Ascertaining the differences between the prior art and the claims at issue.
    3. Resolving the level of ordinary skill in the pertinent art.
    4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Examiner had clearly shown that there is equivalency teaching of the exemplified pyridopyrimidne with pyrrolopyrimidne claimed in Cockeriil et al.

Examiner had shown that Cockerill et al teaches use of the compounds as tyrosine kinase inhibitors for treating psoriasis.

Thus one trained in the art would be motivated to make the pyrrolopyrimidne and expect that it would have the same activity as pyridopyrimidine.

Applicants have not provided any evidence why one trained in the art would not do so.

Applicants also argue that citing In re Baird, there is no guidance provided to select pyrrolo group. This is also not a tenable argument.

As noted in the previous office action Cockerill et al permits A to be various heterocyclic ring, which is clearly defined to indicate what is included. See page 11.

The said pyrrolo ring is the 4th choice and the exemplified pyridine ring is the 8th choice. Thus there is guidance as to what to choose.

Again on page 16, Cockerill et al teaches pyridine, pyrimidine, pyrrole, furan and thiophene as preferred embodiment of ring A.

Given these facts, one trained in the art would know that any one of the choices explicitly recited would possess the utility taught by the art and therefore would be motivated to make compound bearing the said A ring.

Thus contrary to applicants urging, citing In re Baird, there is guidance.

The rejection is proper and is maintained.

Claims 1, 22, 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buzzetti et al. EP 0 795 556 for reasons of record.

Applicants' argument to overcome this rejection is not persuasive.

1. First of all, applicants' argument that examiner had not made a prime facie case is incorrect. The rejection is based on proper factual analysis. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) as noted before is applied.
2. As noted in the previous office action, Buzzetti et al. clearly teaches the equivalency of exemplified 4-NH-hetrocycloalkyl group shown in examples 1-6 with those contemplated and claimed in the definition of various groups of formula I. See formula I on page 2 and note the definition of X, A, R, R_1, R_2, R_3,

R_4 and n. Buzzetti et al. also teaches these compounds are tyrosine kinase inhibitors useful for angiogenesis and as antimetastic agents. See page 6, last paragraph. Hence both motivation and expectation requirements are met with.

3. Applicants' argument that "A" group of Buzzetti et al. meet instant requirement of (C_3-C_9)heterocycloalkyl group, is incorrect. First of all, the definition of (C_3-C_9)heterocycloalkyl group is non-limiting. Note the "etc." at the end of the definition permits any (C_3-C_9)heterocycloalkyl group. Note also the original definition included dihydrofuranyl and chromenyl. The indole and oxyindole of Buzzetti et al. are therefore acceptable as C_3-C_9)heterocycloalkyl group.

Hence the rejection is proper and is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2,19, 22 and 25-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim1-2, 20 and 22-29 of copending Application No. 09/09/891,028. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter embraced in the instant claims is also embraced in the copending application. Compare R^5 group of instant claims with copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1,19, 22 and 25-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim1-12 of copending Application No. 09/956,645. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter embraced in the instant claims is also embraced in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' argument that instant R^5, which requires heteroatom, is not embraced in 09/956,645, is incorrect. There are several groups, which overlap. For example, the

generic definition of heterocycloalkyl would include piperazinyl alkyl embraced in the copending application. Hence this rejection is maintained.

References cited in the Information Disclosure Statement (paper # 11) are made of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

1/09/2003